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Unusually Reactive and Selective Carbonyl Ylides for Three-Component Cycloaddition Reactions

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Abstract: Conditions are described for the Rh-catalyzed formation of highly functionalized dihydro- and tetrahydrofuran products via three-component reactions of aldehydes, α-alkyl-α-diazoesters, and dipolarophiles. The alkyl-substituted carbonyl ylides that are generated in this fashion are highly reactive in cycloaddition reactions and display a scope of reactivity that is much broader than the three-component reactions of carbonyl ylides derived from ethyl diazoacetate or α-aryl-α-diazoesters. The reactions of alkyl-substituted carbonyl ylides proceed with high regioselectivity and diastereoselectivity that are rationalized in terms of an asynchronous, *endo*-selective transition state.

Introduction

Dipolar cycloadditions are powerful reactions that rapidly build structurally complex heterocycles, and the multicomponent nature of dipolar cycloaddition reactions has been used to great effect in discovery chemistry.[1] Metal-catalyzed cycloadditions involving carbonyl ylides can generate stereochemically complex products from three simple starting materials.[2] The scope of such cycloadditions is broad when carbonyl ylides are formed by intramolecular processes.[2] In contrast, analogous three-component reactions involving aldehydes, diazo compounds, and dipolarophiles had been relatively limited in terms of selectivity and substrate scope.[3] Because of competing dioxolane formation,[3a,4,5] the scope is generally limited to highly activated dipolarophiles (e.g., maleate), and mixtures of regio- and stereoisomers are often obtained.

In an elegant study, Jamison and co-workers[3e] investigated the Rh-catalyzed reactions of carbonyl ylides derived from trimethylsilyldiazomethane and dicobalt hexacarbonyl complexes of propargyl aldehydes. The Jamison system exhibited high diastereoselectivity and a broad substrate scope. However, regioselectivity was an issue for many of those transformations.[3e] Muthusamy et al.[3f] described Rh-catalyzed reactions of cyclic diazoamides, aldehydes, and dimethyl acetylenedicarboxylate that proceed with high diastereoselectivity, but the regioselectivity was low when ethyl acrylate was substituted as the dipolarophile. Nair et al.[3g] demonstrated that reactions of diazomalonate, aromatic aldehydes, and β-nitrostyrene proceed with high regio- and stereocontrol. Despite these considerable advances, there was still not a general three-component method for combining aldehydes, diazo compounds, and dipolarophiles with broad scope and control over regio- and diastereoselectivity. Accordingly, we sought to develop three-component reactions that would parallel the large scope of cycloadditions with cyclic carbonyl ylides.[2]

We recently demonstrated that carbonyl ylides of structure **1** could be generated from α-alkyl-α-diazoesters at low temperature with catalytic dirhodium tetrapivalate (Rh_2Piv_4).[4f] Such ylides were not previously accessible because of the propensity of the precursor Rh carbenoids to undergo β-hydride elimination.[6] Ylides **1** were shown to react with excess aldehyde at

(1) (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (b) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. (c) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley: New York, 1998. (d) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. (e) Mehta, G.; Muthusamy, S. *Tetrahedron* **2002**, *58*, 9477.

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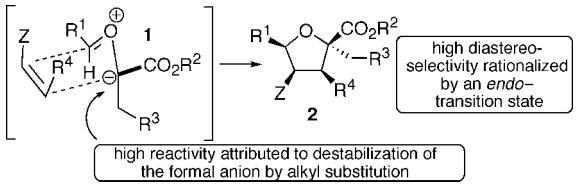
(3) (a) de March, P.; Huisgen, R. *J. Am. Chem. Soc.* **1982**, *104*, 4952. (b) de March, P.; Huisgen, R. *J. Am. Chem. Soc.* **1982**, *104*, 4953. (c) Alt, M.; Mass, G. *Tetrahedron* **1994**, *50*, 7435. (d) Lu, C.-D.; Chen, Z.-Y.; Liu, H.; Hu, W.-H.; Mi, A.-Q.; Doyle, M. P. *J. Org. Chem.* **2004**, *69*, 4856. (e) Skaggs, A. J.; Lin, E. Y.; Jamison, T. F. *Org. Lett.* **2002**, *4*, 2277. (f) Muthusamy, S.; Gunanathan, C.; Nethaji, M. *J. Org. Chem.* **2004**, *69*, 5631. (g) Nair, V.; Mathai, S.; Varma, R. L. *J. Org. Chem.* **2004**, *69*, 1413. For the stereospecific synthesis of tetrahydrofuran derivatives by the Lewis acid catalyzed cycloadditions of aldehydes and donor-acceptor cyclopropanes, see: (h) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642.

(4) (a) Doyle, M. P.; Forbes, D. C.; Protopopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R. *J. Org. Chem.* **1997**, *62*, 7210. (b) Russell, A. E.; Brekan, J.; Gronenberg, L.; Doyle, M. P. *J. Org. Chem.* **2004**, *69*, 5269. (c) Jiang, B.; Zhang, X.; Luo, Z. *Org. Lett.* **2002**, *4*, 2453. (d) Alt, M.; Mass, G. *Tetrahedron* **1994**, *50*, 7435. (e) Wenkert, E.; Khatuya, H. *Tetrahedron Lett.* **1999**, *40*, 5439. (f) DeAngelis, A.; Panne, P.; Yap, G. P. A.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 1435.

(5) For three-component dioxolane formation, see: (a) Nair, V.; Mathai, S.; Nair, S. M.; Rath, N. P. *Tetrahedron Lett.* **2003**, *44*, 8407. (b) Nair, V.; Mathai, S.; Mathew, S. C.; Rath, N. P. *Tetrahedron* **2005**, *61*, 2849. (c) Lu, C.-D.; Chen, Z.-Y.; Liu, H.; Hu, W.-H.; Mi, A.-Q. *Org. Lett.* **2004**, *6*, 3071.

Scheme 1. Cycloadditions of Alkyl-Substituted Carbonyl Ylides



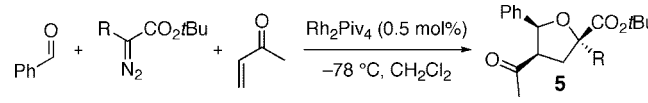
−78 °C to produce dioxolanes with high diastereoselectivity. We reasoned that the alkyl substituents of **1** destabilize the formal negative charge on the ylide and consequently that ylides **1** should display enhanced reactivity toward exogenous dipolarophiles (Scheme 1). Herein, it is demonstrated that Rh_2Piv_4-catalyzed three-component reactions of aldehydes, α-alkyl-α-diazoesters, and dipolarophiles give a diverse range of tetrahydrofuran (**2**) or dihydrofuran products (Scheme 1) with an unusually broad reaction scope and high selectivity. The high regio- and diastereoselectivity is rationalized by the asynchronous endo transition state displayed in Scheme 1.

Results and Discussion

Rh_2Piv_4 has previously been shown[4f] to be an efficient catalyst for the formation of carbonyl ylides from α-alkyl-α-diazoesters and benzaldehyde derivatives. It was found that methyl vinyl ketone was able to intercept the carbonyl ylide generated from benzaldehyde and *tert*-butyl 2-diazohydrocinnamate in the presence of Rh_2Piv_4 at −78 °C to form the functionalized tetrahydrofuran product with high regio- and diastereoselectivity. Following an optimization study (Table 1), it was found that the yields were highest when benzaldehyde was used as the limiting reagent with small excesses of *tert*-butyl 2-diazohydrocinnamate and methyl vinyl ketone. However, when these conditions were applied to the analogous system with *tert*-butyl 2-diazopropanoate, the reaction did not go to completion and the yields were lower. For this system, as well as for others in which the diazoester is substituted with a simple alkyl chain (R = Me, Bu), it was necessary for 1.7 equiv of diazo compound to be used in order to push the reaction to near-completion. Hashimoto's dirhodium tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] catalyst[7] was tested for asymmetric induction in the reaction of *p*-anisaldehyde, *tert*-butyl 2-diazohydrocinnamate, and methyl vinyl ketone, but the product obtained was racemic. $Rh_2(OAc)_4$ and $Cu(acac)_2$ were also examined as catalysts in the reaction between methyl vinyl ketone, benzaldehyde, and *tert*-butyl 2-diazohydrocinnamate at −78 °C. β-Hydride elimination predominated with $Rh_2(OAc)_4$, and tetrahydrofuran **5** (R = Bn) was obtained in less than 20% yield. The tetrahydrofuran products were not formed at all in the reaction with $Cu(acac)_2$, which lead to products that we have not yet been able to identify.

The conditions from Table 1 were applied to a variety of alkynes and alkenes with a single activating group to give products **3**−**7** (Scheme 2). Successful reactivity was observed for α-diazopropionate, α-diazobutanoate, α-diazooctanoate,

Table 1. Optimization Study[a]



entry	PhCHO (equiv)	Diazo compound (equiv)		methyl vinyl ketone (equiv)	yield of **5**[b]
1	1.1	1.0	R=Bn	4.0	53%
2	1.0	1.5		4.0	78%
3	1.0	2.0		4.0	78%
4	1.0	1.5		2.0	85%
5	1.0	1.5		1.1	81%
6	**1.0**	**1.3**		**1.1**	**84%**
7	1.0	1.1		1.1	76%
8[c]	1.0	1.5		1.1	16%
9	1.0	1.3	R=Et	1.1	56%
10	1.0	1.5		1.1	69%
11	**1.0**	**1.7**		**1.1**	**77%**
12	1.0	1.9		1.1	76%

[a] Optimal conditions are highlighted in bold print. [b] NMR yield. [c] Reaction was carried out at room temperature.

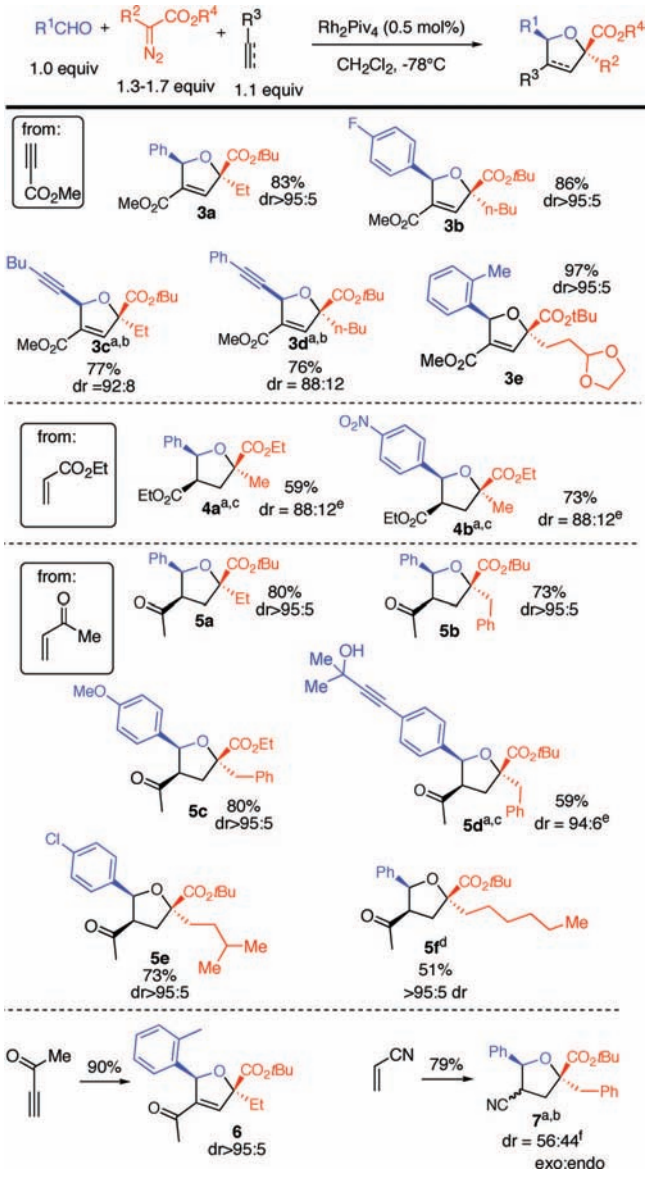
α-diazo-5-methylhexanoate, α-diazo-4-[1,3]dioxolan-2-yl-butanoate, and α-diazohydrocinnamate with a range of aromatic aldehydes or with propargyl aldehydes. The dipolarophiles include methyl propiolate, ethyl acrylate, methyl vinyl ketone, acrylonitrile, and propargyl methyl ketone. Prior use of such dipolarophiles in three-component reactions with carbonyl ylides had been limited, and in those instances, ≤3:1 regioselectivity was observed.[3e,f] The three-component reactions in Scheme 2 generally proceeded with excellent selectivity: high selectivity (>88:12) was observed for 11 of the 12 examples in Scheme 2, and only one isomer (>95:5) was observed in seven cases. The exceptional case was the reaction of acrylonitrile, benzaldehyde, and *tert*-butyl 2-diazohydrocinnamate, which proceeded to give **7** with high regioselectivity but poor stereoselectivity. For the formation of **5f**, cyclopentane formation via intramolecular C−H activation was a competing side reaction, but the use of excess benzaldehyde (4.0 equiv) and dipolarophile (4.0 equiv) did give **5f** in acceptable yield (51%). In contrast, intramolecular C−H activation was not a competing side reaction for the formation of **5e** from *tert*-butyl α-diazo-5-methylhexanoate.

More highly substituted dipolarophiles also combine efficiently with alkyl-substituted carbonyl ylides to give products **8**−**17**, as shown in Scheme 3. Of the dipolarophiles in Scheme 3, only maleic anhydride and dimethyl acetylenedicarboxylate have been utilized previously[2c,3b,4a] in three-component reactions involving carbonyl ylides. Unsymmetrical dipolarophiles also react efficiently with alkyl-substituted carbonyl ylides: the reactions of cyclohexenone, methyl methacrylate, and dimethyl 2-ethylidenemalonate proceed with high regioselectivity to give **8**, **11**, and **17**, respectively. Diethyl azodicarboxylate successfully leads to the tetrahydrooxa-3,4-diazole **10**. Strain can also be used to activate dipolarophiles:[3e,8] prochiral cyclopropene **13** and chiral cyclopropene **15** react efficiently to give **14** and **16**, respectively. Excellent regio- and diastereoselectivity (>95:

(6) For the Rh-catalyzed preparation of (*Z*)-alkenes via β-hydride elimination, see: (a) Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908, and references therein. For recent studies on suppressing β-hydride elimination through ligand selection, see ref 4f and: (b) Panne, P.; DeAngelis, A.; Fox, J. M. *Org. Lett.* **2008**, *10*, 2987. (c) Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22.

(7) (a) Minami, K.; Saito, H.; Tsutsui, H.; Nambu, H.; Anada, M.; Hashimoto, S. *Adv. Synth. Catal.* **2005**, *347*, 1483. (b) Tsutsui, H.; Abe, T.; Nakamura, S.; Anada, M.; Hashimoto, S. *Chem. Pharm. Bull.* **2005**, *10*, 1366.

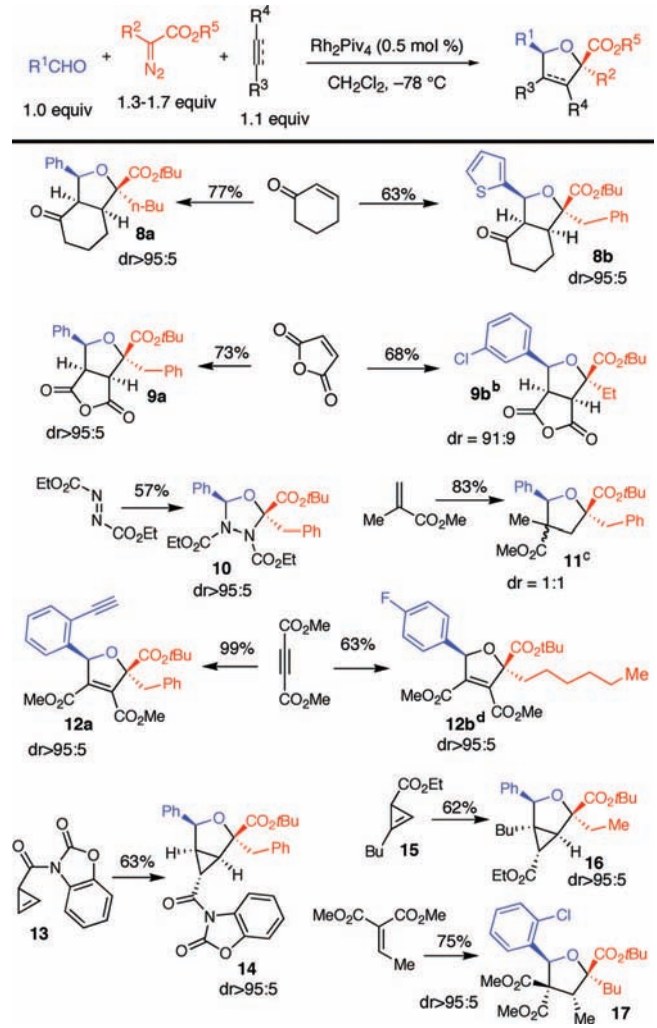
Scheme 2. Three-Component Coupling Reactions of Dipolarophiles with a Single Activating Group



[a] Two diastereomers were detected upon analysis of the ^{1}H NMR spectrum of the crude product. Other isomeric materials were not detected. [b] Yield of both diastereomers. [c] Yield of the diastereomer shown. [d] The reaction was carried out with 1.0 equiv of *t*-butyl α-diazooctanoate, 4.0 equiv of benzaldehyde, and 4.0 equiv of methyl vinyl ketone. [e] The relative stereochemistry of the minor isomer was not determined. [f] Stereochemical assignments were made on the basis of ^{1}H NMR analysis (see the Supporting Information).

5) was observed in all cases in Scheme 3 except for the reaction of methyl methacrylate, which gave **11** with 1:1 diastereoselectivity, and the reaction of maleic anhydride, which gave **9b** with 91:9 diastereoslectivity. A variety of functional groups are tolerated by the reactions in Schemes 2 and 3, including esters, alkynes, nitriles, oxazolidinones, alcohols, and nitro and methoxy groups.[9] As in the formation of **5f**, cyclopentane formation via intramolecular C−H activation was a competing side reaction for the formation of **12b**. However, the use of excess

Scheme 3. Three-Component Coupling Reactions of Dipolarophiles with Multiple Substitutents[a]



[a] Diastereomer ratios were determined by analysis of the ^{1}H NMR spectra of the crude product; no other isomeric materials were observed. Stereochemical assignments were made on the basis of ^{1}H NMR analysis (see the Supporting Information). [b] Isolated yield of diastereomer shown. [c] Isolated yield of both diastereomers. [d] The reaction was carried out with 1.0 equiv of *t*-butyl α-diazooctanoate, 4.0 equiv of 4-fluorobenzaldehyde, and 4.0 equiv of dimethyl acetylenedicarboxylate.

4-fluorobenzaldehyde (4.0 equiv) and dipolarophile (4.0 equiv) gave **12b** in good yield (63%).

The reactions in Schemes 2 and 3 are subject to some limitations. Attempts to use 1-hexene, phenyl acetylene, norbornene, and vinyl trimethylsilane were unsuccessful and led primarily to dioxolane products. An attempt to utilize *tert*-butyl α-diazoisovalerate led only to β-hydride elimination. Reactions with dimethyl maleate, ethyl *trans*-crotonate, 3-pentyn-2-one, and acrolein gave the desired products in very low yield (≤10%). When alkyl aldehydes (propionaldehyde and pivaldehyde) were used, only β-hydride elimination was observed. An attempt to utilize *tert*-butyl α-diazo-α-cyclohexylacetate led only to β-hydride elimination.

The generation and rapid reactivity of alkyl-substituted carbonyl ylides at low temperature is the key to selective

(8) For reactions of carbonyl ylides with cyclopropenes, see: Diev, V. V.; Kostikov, R. R.; Gleiter, R.; Molchanov, A. P. *J. Org. Chem.* **2006**, *71*, 4066.

(9) We note that functional group tolerance was initially guided by an inhibition study in which various functionalized molecules were added in superstoichiometric amounts to the reaction between *tert*-butyl 2-diazohydrocinnamate, benzaldehyde, and methyl vinyl ketone (see the Supporting Information).

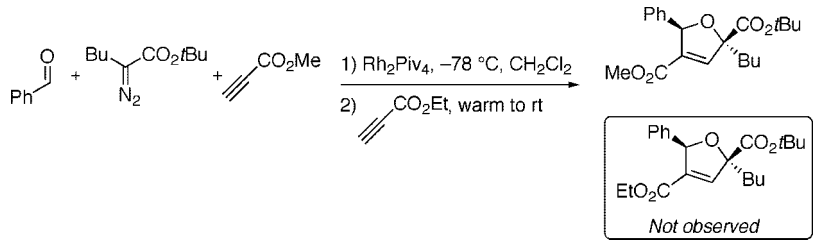


Figure 1. Mixing experiment.

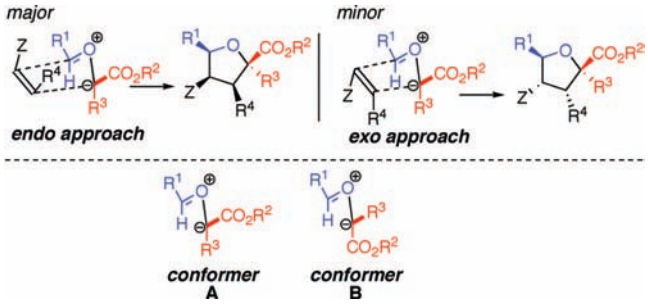


Figure 2. Proposed model to explain the diastereoselectivity.

reactivity. At higher temperatures, the selectivities and yields are poor. When *tert*-butyl 2-diazohydrocinnamate was reacted with benzaldehyde and methyl vinyl ketone at room temperature (rt), the tetrahydrofuran product was formed in only 16% yield (Table 1), while the amount of β-hydride elimination (68% based on the diazo compound) increased. Analogous reactions of ethyl diazoacetate or methyl phenyldiazoacetate with benzaldehyde and ethyl acrylate are less successful at −78 °C or rt: The reaction with ethyldiazoacetate formed primarily diethyl maleate and diethyl fumarate at −78 °C or rt. The reaction with methyl phenyldiazoacetate formed the desired product in low yield (31% based on ^{1}H NMR analysis) with competing epoxide[10] formation (18%); the remainder of the mass balance was unreacted aldehyde (16%) and a complex mixture of products.

To demonstrate that the cycloaddition was complete at −78 °C, the reaction of benzaldehyde, *tert*-butyl 2-diazohexanoate, and methyl propiolate was carried out according to the general procedure (Figure 1). Following the addition of the diazo compound, the reaction was allowed to stir at −78 °C for 5 min; after this, ethyl propiolate (1.1 equiv) was added, and the reaction was allowed to warm to room temperature. Analysis of the crude ^{1}H NMR spectrum revealed that cycloaddition had occurred only with methyl propiolate. A control experiment was run in which both methyl propiolate (1.1 equiv) and ethyl propiolate (1.1 equiv) were added prior to diazo addition. Crude ^{1}H NMR analysis revealed a ∼1:1 mixture of the two cycloadducts.

Regio- and stereochemical assignments were made on the basis of X-ray crystal structures for compounds **5b**, **9a**, and **14**; NOE experiments on **17** and the two diastereomers of compound **3c**; and chemical shift anisotropy analysis of the ^{1}H NMR spectra for all of the compounds. In the majority of the cases studied, the major product arises from an endo approach of the dipolarophile to the ylide conformer **A** (Figure 2). An exceptional case was compound **17** derived from dimethyl 2-ethylidenemalonate, in which the major product was formed by exo approach to conformer **A**. Exo/endo isomers were also observed for **7** and **11**, in which the dipolarophiles were acrylonitrile and methyl methacrylate, respectively. Products arising from cycloaddition with the minor ylide conformer, conformer **B**, were observed for **3c** and **3d**, where propargyl aldehydes were employed. The minor isomers of **4a**, **4b**, **5d**, and **9b** were not definitively assigned, but by analogy to our prior observations of dioxolane formation,[4f] we assume that they also arise from endo approach of the dipolarophile to the minor ylide conformer **B**.

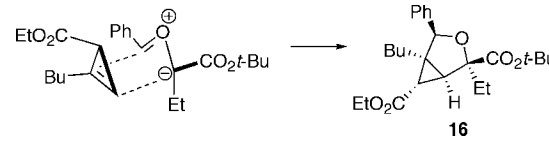


Figure 3. Proposed model for the formation of **16**.

When cyclopropenes **13** and **15** are used as dipolarophiles, the cyclopropene controls the endo selectivity of the cycloadditions to provide the cycloaddition adducts **14** and **16**, respectively, as single diastereomers. The sense of diastereoselectivity is in accord with that observed by Molchanov and co-workers[8] in reactions between cyclic carbonyl ylides and substituted cyclopropenes. With the trisubstituted cyclopropene **15**, the regioselectivity of dipolar cycloaddition is apparently controlled by steric considerations: the preferred regioisomer is derived from the transition state in which the less substituted end of the cyclopropene is aligned with the more substituted end of the carbonyl ylide, as shown in Figure 3.

Conclusions

In summary, general conditions are described for the Rh-catalyzed formation of highly functionalized dihydro- and tetrahydrofurans via three-component reactions of aldehydes, α-alkyl-α-diazoesters, and dipolarophiles with selectivity over dioxolane formation. Alkyl-substituted carbonyl ylides are highly reactive in such transformations, and the scope of reactivity is broad relative to analogous carbonyl ylides derived from ethyl diazoacetate or α-aryl-α-diazoesters. Products are formed in good yields and with excellent regio- and diastereoselectivity when the reactions are carried out at −78 °C in the presence of catalytic Rh_2Piv_4. A model invoking an asynchronous endo transition state is proposed to explain the nature of the diastereoselectivity.

Experimental Section

Representative Procedure for Three-Component Dipolar Cycloaddition Reactions: Synthesis of *rel*-(2*R*,5*R*)-4-Acetyl-2-ethyl-5-phenyltetrahydrofuran-2-carboxylic Acid Ethyl Ester (5a). In a flame-dried round-bottom flask, Rh_2Piv_4 (1.5 mg, 0.002 mmol), benzaldehyde (54 mg, 0.51 mmol), and methyl vinyl ketone (39 mg, 0.56 mmol) were dissolved in anhydrous CH_2Cl_2 (2.5 mL)

(10) Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett.* **2001**, *3*, 933. (b) Davies, H. M. L.; DeMesse, J .*Tetrahedron Lett.* **2001**, *42*, 6803.

and cooled by a bath of dry ice/acetone (−78 °C) under a nitrogen atmosphere. *tert*-Butyl 2-diazobutanoate (146 mg, 0.86 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) and added to the reaction mixture over 1 h via syringe pump. After the addition was complete, the reaction mixture was allowed to stir for an additional 5 min and was then allowed to warm to room temperature. Mesitylene (61 mg, 0.51 mmol) was added to the reaction mixture, and an ^{1}H NMR spectrum was taken to estimate the yield and isomer ratio(s). The solvent was subsequently removed, and the residue was chromatographed on silica gel to give 123 mg (0.39 mmol, 76%) of **5a** as a colorless oil. A similar experiment starting with 50 mg (0.47 mmol) of benzaldehyde, 37 mg (0.52 mmol) of methyl vinyl ketone, and 136 mg (0.80 mmol) of *tert*-butyl 2-diazobutanoate gave 124 mg (0.39 mmol, 83%) of **5a**. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.43−7.38 (m, 2H), 7.33−7.21 (m, 3H), 5.32 (d, J = 7.2 Hz, 1H), 3.46 (app dt, J = 7.6, 3.5 Hz, 1H), 2.85 (dd, J = 13.5, 3.5 Hz, 1H), 2.07 (dd, J = 13.3, 7.4 Hz, 1H), 2.00−1.88 (m, 1H), 1.82−1.72 (m, 1H), 1.59 (s, 9H), 1.42 (s, 3H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 207.2 (u), 172.6 (u), 138.1 (u), 128.4 (dn), 128.0 (dn), 126.5 (dn), 87.0 (u), 82.9 (dn), 81.0 (u), 57.0 (dn), 37.8 (u), 32.4 (u), 30.5 (dn), 28.0 (dn), 8.58 (dn). IR ($CHCl_3$, cm^{-1}): 2981, 2937, 1731, 1714, 1615, 1457, 1370, 1254, 1124, 1061, 908, 845, 701, 662. HRMS-ESI for [M + Na] (m/z): calcd for $C_{19}H_{26}O_4Na$, 341.1729; found, 341.1719.

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Supporting Information Available: Experimental and characterization details, ^{1}H and ^{13}C NMR spectra for the new compounds, a description of stereochemical assignments, results of NOE experiments on **17** and the two diastereomers of compound **3c**, and CIF files for **5b**, **9a**, **12**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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